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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/506,301	12/16/2004	Ganapathy Gopalrathnam	X-15199	3398

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EXAMINER	
BARNHART, LORA ELIZABETH	
ART UNIT	PAPER NUMBER
1651	

SHORTENED STATUTORY PERIOD OF RESPONSE	NOTIFICATION DATE	DELIVERY MODE
3 MONTHS	02/01/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Notice of this Office communication was sent electronically on the above-indicated "Notification Date" and has a shortened statutory period for reply of 3 MONTHS from 02/01/2007.

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patents@lilly.com

Office Action Summary	Application No.	Applicant(s)	
	10/506,301	GOPALRATHNAM ET AL.	
	Examiner	Art Unit	
	Lora E. Barnhart	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,11,12 and 14-24* is/are pending in the application.

4a) Of the above claim(s) *20-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,11,12,14-19 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendments

Applicant's amendments filed 11/20/06 to claims 1, 11, 14, and 24 have been entered. Claims 2-10 and 13 have been cancelled. Claims 1, 11, 12, and 14-24 remain pending in the current application, of which claims 1, 11, 12, 14-19, and 24 are being considered on their merits. Prior art references not included with this Office action can be found in a prior action.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/20/06 has been entered.

Claim Objections

Claim 1 is objected to because of the following informalities: It recites the abbreviation "I.V." without defining the same. For purposes of clarity, the examiner suggests the claim be amended to replace "I.V." with "intravenous delivery bag" or the like.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 11, 12, 14-19, and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is drawn to a composition that "has reduced or eliminated any increase in 1-149 aPC light chain variant 24 hours after preparation of the composition," which is confusing because the claim appears to recite active method steps. It is not clear whether the claim is limited to a composition or whether it means to include a process or preparation comprising "reducing" or "eliminating" steps. Clarification is required. Claim 11 suffers similar deficiencies. Because claims 12, 14-19, and 24 depend from indefinite claim 1 and do not clarify the point of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

In the interest of compact prosecution, claim 1 has been interpreted as being drawn to a pharmaceutical composition "which, 24 hours after its preparation, comprises reduced levels of 1-149 aPC light chain variant compared to some standard or no 1-149 aPC light chain variant." Similarly, claim 11 has been interpreted as being drawn to a pharmaceutical composition "which, 24 hours after its preparation, comprises levels of 1-149 aPC light chain variant no greater than 2% higher than some standard."

Claim 17 refers to conditions "upon reconstitution," which is confusing because claim 1 has been amended to limit the composition to a liquid composition by its requirement of a "diluent," which is defined as an agent that makes thinner or more liquid by admixture (Merriam-Webster OnLine Dictionary; reference U). It is not clear

what steps would be considered "reconstitution" in light of the claim amendments. Clarification is required. In the interest of compact prosecution, the limitations of claim 17 have been interpreted as describing the pH of the claimed liquid composition.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 11, 12, and 14-19 remain rejected under 35 U.S.C. 102(b) as being anticipated by Carlson et al. (2000, U.S. Patent 6,159,468; IDS reference AU) taken in light of Voet et al. (1995, *Biochemistry*, 2nd ed.). The claims are drawn to a pharmaceutical composition comprising activated protein C (aPC), a chelating agent, and a diluent, wherein the composition is contained in a vial or bag, is suitable for administration to a patient, and has reduced levels of 1-149 aPC light chain variant ("1-149"). In some dependent claims, the composition further comprises a bulking agent, which may be selected from a list; further comprises a buffer selected from a list, which may provide a specific pH; further comprises a salt, which may be selected from a list; or further comprises a diluent, which may have particular properties.

Carlson et al. teach a composition comprising human protein C, 0.4M sodium chloride, and 20mM Tris-acetate, pH 6.5 (Preparation 1); Preparation 1 is made 5mM in EDTA and passed over a thrombin column, thus activating protein C, then passed over an anion exchange column to remove thrombin (which flows through such columns) and

eluted with Tris buffer and lyophilized (Preparation 2). Preparation 2 therefore comprises activated protein C (aPC), EDTA (a chelator; see column 7, lines 1-2), Tris-acetate, and sodium chloride at pH 6.5 (a diluent; column 7, lines 26-27; Example 1). Carlson et al. further teach dissolving lyophilized Preparation 2 in phosphate buffer, then adding a bulking agent (either mannitol, sucrose, trehalose, or raffinose) and re-lyophilizing (Examples 1 and 2). Voet et al. is cited as evidence that polyanions such as EDTA (ethylenediamine tetraacetate) reversibly bind to anion exchangers (*i.e.*, they do not flow through, but rather stay on the column with the aPC); therefore, Preparation 2 of Carlson et al. comprises EDTA. Finally, Carlson et al. teach that their composition is suitable for administration to a patient ((column 5, lines 38-58).

While Carlson et al. do not explicitly teach that their Preparation 2 is contained in a "vial or I.V. bag," the person of ordinary skill in the art would have appreciated that this was, in fact, the case. A vial is defined as "a small closed or closeable vessel, especially for liquids" (Merriam-Webster OnLine Dictionary; reference U). Carlson et al. make numerous references to preparing samples and solutions (for example, at column 8, lines 44-51); the skilled artisan would certainly appreciate that liquids in the laboratory must be stored in some sort of vessel, for example a test tube. A test tube is a closeable vessel for liquids and, therefore, is included in the plain-words definition of "vial."

M.P.E.P. § 2112.01 recites, "Products of identical chemical composition can not have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present." See *In re Spada*

(citations omitted). The composition of Carlson et al. and the instantly claimed composition both comprise aPC, a chelating agent, and a diluent; since the compositions have identical components, they are identical and, therefore, have identical physical and chemical properties. While Carlson et al. do teach the reduction or elimination of 1-149 increase in the composition after 24 hours of storage as instantly claimed, their composition is identical to the instant composition **as claimed** and, therefore, necessarily possesses this property. It is worth noting that Carlson et al. teach that their composition is "substantially free of [undesired] autodegradation products" (column 2, lines 1-6).

Applicant alleges that Carlson et al. do not teach a composition that has reduced or eliminated 1-149 increase 24 hours after it has been prepared (Reply, page 5, paragraph 1). Applicant alleges that the aPC formulation of Carlson et al., which contains "some EDTA," is similar to the composition exemplified in Preparation 2 of the instant application and that such compositions for 1-149 (Reply, page 5, paragraph 2). These arguments have been fully considered, but they are not persuasive.

As discussed above, the composition of Carlson et al. is identical to the instant composition **as claimed** and, therefore, inherently possesses identical properties, absent some evidence to the contrary. Applicant alleges that such evidence is present in the specification (Tables 1A and 1B at pages 14 and 15). However, claim 1 requires "reduced" formation of 1-149 over the 24-hour storage period, but it provides no specific basis for comparison for this relative term. Because claim 1 contains no basis for

comparison, any formulation that contains less 1-149 than some other formulation would fulfill the requirements.

Applicants stipulate that the composition of Carlson et al., like the first three formulations in Table 1A (specification, page 14), contains "some" EDTA but that the amount of EDTA in these compositions is insufficient to yield a composition with the claimed properties (Reply, page 7, paragraph 1). However, an examination of Table 1A in light of the broad nature of claim 1 indicates that this is not the case. The second formulation in Table 1A ("24-hour...with freshly prepared 0.9% sodium chloride solution (control)") contains 59% 1-149, while the second formulation in Table 1B ("24-hour...in 150mL PVC IV bag of 0.9% sodium chloride solution (control)") contains 78% 1-149. Therefore, the residual EDTA in the Table 1A formulation is sufficient to prevent 1-149 formation relative to the Table 1B formulation. Applicant is incorrect in arguing that the amount of EDTA in the composition of Carlson et al. (which applicant stipulates is similar to the amount in their Table 1A and 1B formulations) is insufficient to prevent 1-149 formation.

Claims 1, 11, and 12 remain rejected under 35 U.S.C. 102(b) as being anticipated by Foster et al. (1996, U.S. Patent 5,516,650; IDS reference AO) taken in light of Carlson et al. (AU). The claim is drawn to a pharmaceutical composition comprising activated protein C and a chelating agent. In some claims, the composition further comprises a diluent.

Foster et al. teach a solution comprising activated protein C, EDTA (a chelating agent), and TBS (Tris-buffered saline) in water (column 21, lines 20-24). Carlson et al. is cited as evidence that Tris is a pharmaceutically acceptable buffer (column 3, lines 9-12). Foster et al. teach that their compositions are suitable for administration to a patient: "The proteins described within the present invention may be used as active therapeutic substances, including use in the regulation of blood coagulation" (column 4, lines 1-3).

The discussions of the "vial or I.V. bag" and "reduction or elimination of 1-149 after 24 hours of storage" limitations in the above rejection over Carlson et al. also apply to this rejection.

Applicant alleges that Foster et al. teach "a method of purifying a ***variant form of activated protein C***" (Reply, page 5, paragraph 4). Applicant alleges that Carlson et al. do not anticipate the claimed composition. These arguments have been fully considered, but they are not persuasive.

Applicant's comments about the teachings of Foster et al. are confusing. The specification places no limit on the scope of "activated protein C" that would eliminate variant forms. The specification teaches, "aPC or activated protein C refers to activated protein C whether recombinant or plasma derived" (page 3, lines 18-19). Foster et al. teach, "protein C produced by [their method] is approximately 100% active relative to plasma protein C" (column 21, lines 45-47). Therefore, the aPC of Foster et al. is within the scope of the definition of aPC set forth in the specification.

The comments regarding the rejection over Carlson et al., above, also apply to this rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-9, 11-19, and 24 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Carlson et al. (2000, U.S. Patent 6,159,468; IDS reference AU). The claims are drawn to a pharmaceutical composition comprising activated protein C and a chelating agent. In some dependent claims, the composition is lyophilized; further comprises a bulking agent, which may be selected from a list; further comprises a buffer selected from a list, which may provide a specific pH; further comprises a salt, which

may be selected from a list; or further comprises a diluent, which may have particular properties.

As discussed above, Carlson et al. teach a composition comprising human protein C, 0.4M sodium chloride, and 20mM Tris-acetate, pH 6.5 (Preparation 1); Preparation 1 is made 5mM in EDTA and passed over a thrombin column, thus activating protein C, and eluted with Tris buffer and lyophilized (Preparation 2). Preparation 2 therefore comprises activated protein C, EDTA (a chelator; see column 7, lines 1-2), Tris-acetate, and sodium chloride at pH 6.5 (column 7, lines 26-27; Example 1). Carlson et al. further teach dissolving lyophilized Preparation 2 in phosphate buffer, then adding a bulking agent (either mannitol, sucrose, trehalose, or raffinose) and re-lyophilizing (Examples 1 and 2). Carlson et al. do not exemplify other buffers or salts.

Carlson et al. teach that mannitol, trehalose, raffinose, and sucrose are all acceptable bulking agents for the composition (column 3, lines 29-30 and 60-63). Carlson et al. further teach that Tris buffers, citrate buffers, phosphate buffers, and acetate buffers are all pharmaceutically acceptable buffers (column 3, lines 9-12, and column 4, lines 20-27). Carlson et al. teach that the pH of the composition, upon reconstitution, is between 5.5 and 6.5 (column 3, lines 30-33). Carlson et al. further teach that potassium chloride and sodium chloride are acceptable salts for inclusion in the composition (column 4, lines 37-41). Carlson et al. teach the importance of removal of residual calcium using chelators, for example EDTA, from protein C preparations (column 6, lines 35-50). Finally, Carlson et al. contemplate the administration of the composition to a patient in need thereof (column 5, lines 38-58).

The selection of bulking agent, salt, and buffer from among the recited species clearly would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that Carlson et al. teach that said species are acceptable substitutes for each other (see above). A holding of obviousness over the cited claims is therefore clearly required.

While the composition of Carlson et al. comprises some EDTA from the activation step (column 7, lines 1-3), a person of ordinary skill in the art would have had a reasonable expectation of success in including additional EDTA in the composition of Carlson et al. because EDTA is taught by Carlson et al. not to affect the composition's essential properties. The skilled artisan would have been motivated to include additional EDTA for the expected benefit that activated protein C would be protected from calcium and other divalent ions. It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to include additional EDTA in the composition of Carlson et al. because Carlson et al. suggest its inclusion to chelate metal ions.

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

Applicant alleges that the skilled artisan would not have been motivated "to add additional EDTA to lyophilized aPC...nowhere does Carlson [et al.] teach or suggest a need for or advantage from additional EDTA in the composition after the purification process and lyophilization" (Reply, page 6, paragraph 2). Applicant alleges that at the time of the invention, the person of ordinary skill in the art would not have added a

chelating agent to prevent degradation of aPC (*ibid.*) and that the prior art does not suggest adding a chelating agent "to improve the solution stability of aPC" (Reply, page 7, paragraph 1).

In response to applicant's argument that Carlson et al. did not recognize the need to prevent 1-149 formation, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). EDTA is a well-known chelating agent that is included in the product of Carlson et al. and that does not interfere with the essential properties of aPC. Carlson et al. specifically teach a step to remove calcium (column 6, lines 36-37). Clearly, Carlson et al. recognized an advantage in removing calcium from their aPC preparation; the fact that Carlson et al.'s motivation for including EDTA in their composition was different from applicant's does not distinguish the instant claims from the cited prior art.

No claims are allowed. No claims are free of the art.

Applicant should specifically point out the support for any amendments made to the disclosure in response to this Office action, including the claims (MPEP 714.02 and 2163.06). Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Applicant is requested to provide a list of all copending U.S. applications that set forth similar subject matter to the present claims. A copy of such copending claims is requested in response to this Office action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora E. Barnhart whose telephone number is 571-272-1928. The examiner can normally be reached on Monday-Thursday, 9:00am - 5:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Lora E Barnhart